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EXAMINER	
GABEL, GAILENE 15	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 03/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/687,051	BUECHLER ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-74 and 79-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *71-74* is/are allowed.

6)☒ Claim(s) *69,70,79-83,86-89,91 and 92* is/are rejected.

7)☒ Claim(s) *84,85,90 and 93* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's response filed 1/8/03 in Paper No. 13 is acknowledged. Currently, claims 69-74 and 79-93 are pending and are under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 102

2. In light of Applicant's arguments, the rejection of claims 79-93 under 35 U.S.C. 102(b) as being anticipated by Bodor et al. (Clinical Chemistry, 1992) is hereby, withdrawn.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 69-70, 79-83, 86-89, and 91-92 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a cocktail of insensitive antibodies, wherein each antibody binds each one of the free cTnI, binary complex of cTnI, and ternary complex of cTnI for use in an assay for determining free and complexed cardiac specific isoforms of troponin (cTnI), does not reasonably provide

enablement for a single insensitive antibody, which binds each one and all of free cTnI, binary complex of cTnI, and ternary complex of cTnI for use in an assay for determining free and complexed cTnI. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As set forth in In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a cocktail of insensitive antibodies which bind each one of the free, binary complex, and ternary complex isoforms of cTnI for use in a method for determining the presence or amount of all free and binary and ternary complexed isoforms of cTnI.

The state of the prior art- the prior art of record fails to disclose an insensitive antibody which binds each and all of the free, binary, and ternary complexed isoforms of cTnI for use in a method for determining the presence or amount of all free, binary and ternary complexed isoforms of cTnI.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that a single insensitive antibody binds each and all of the free, binary, and ternary complexed isoforms of cTnI for use in a method of determining the presence or amount of all of the free, binary and ternary complexed isoforms of cTnI in a sample.

The amount of direction or guidance present- appropriate guidance is provided by the specification for a cocktail of insensitive antibodies that have been generated to specifically bind each one of the free, binary, and ternary complexed isoforms of cTnI for use in a method to determine the presence or amount of all of the free, binary and ternary complexed isoforms of cTnI in a sample. However, the specification fails to provide guidance to provide a single insensitive antibody that specifically binds all of the free, binary and ternary complexed isoforms of cTnI to determine the total concentration of a cTnI isoform the claimed in an assay.

The presence or absence of working examples- working examples are provided in the specification that show a cocktail of insensitive antibodies that bind each one of the free, binary, and ternary complexed isoforms of cTnI for use in determining all of the free, binary and ternary complexed isoforms of cTnI in a sample. There are no working

examples that show analogous results using a single insensitive antibody, which is encompassed by the broad scope of the instant claims.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a single insensitive antibody that binds all of the free, binary and ternary complexed isoforms of cTnI for use in a method of determining the presence or amount of all free, binary, and ternary complexed isoforms of cTnI in a sample. As recited, the instant single insensitive antibody has specific binding for each of the free, binary, and ternary complexed isoforms of cTnI and is capable of determining the presence or amount of all of free, binary, and ternary complexed isoforms of cTnI in as sample.

In this case, the specification at pages 6-7 describes antibodies for use in the claimed method that are monoclonal, polyclonal, fragment thereof, and recombinant . These antibodies are characterized as being "sensitive" or "insensitive", the sensitive antibodies tend to bind and exhibit preferential detection of a single form of troponin and the insensitive antibodies tend to bind and exhibit detection of more than one form of troponin. In pages 13-14, the specification shows that an insensitive antibody is utilized to bind to the free and complexed forms of troponin; that is, insensitive with respect to the oxidized, reduced, and complexed forms of troponin. Alternatively, more than one sensitive antibody would be necessary to measure both the free and complexed forms of troponin. At pages 21-22, the specification shows how to generate and select

antibodies that are sensitive or insensitive to the binding of free troponin I or T, troponin I or T in binary complexes, and troponin I or T in ternary I/T/C complexes; this is accomplished by purification of free troponin I or T, binary troponin I/T, T/C, and I/C complexes and ternary I/T/C complexes, respectively, then injection into mice or rabbits to generate monoclonal or polyclonal antibodies. The antibodies are then screened for affinity and specificity with the purified free troponin, binary complexes of troponin, and ternary complexes of troponin.

While the specification at pages 29-31 exemplifies selected antibodies, i.e. a cocktail of antibodies, that bind one of the free cTnI, binary complexed cTnI, and ternary complexed cTnI, for use in the claimed method of determining the amount of free, binary complexed, and ternary complexed cTn, the specification does not show any working examples of a single insensitive antibody that has binding for all of the free cTn, binary complexed cTn, and ternary complexed cTn. The fact that insensitive antibodies that bind more than one form of cTnI has been characterized, is not sufficient to enable the breadth of the claimed method to use a single insensitive antibody in an assay to determine the presence or amount of all of free cTn, binary complexed cTn, and ternary complexed cTn. The specification does not establish a direct correlation between using a cocktail of insensitive and/or sensitive antibodies and a single "insensitive" antibody, which would lead the skilled artisan to say that the claimed method works for a single insensitive antibody to enable the breadth of the claimed method. The specification does not provide any teaching that suggests that an antibody generated against purified free cTnI, an antibody generated against purified binary complexed cTnI, or an antibody

generated against purified ternary complexed cTnI, can be characterized to bind a conserved epitope for each and all of said free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample. Further, the working examples at Example 15 and Example 16, also utilize a cocktail of insensitive antibodies to determine the presence or amount of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample. While it is not necessary to show working examples for every possible embodiment, there should be sufficient teachings in the specification that would suggest to the skilled artisan that the breadth of the claimed method is enabled. This is not the case in the instant specification. Thus, the claimed method is only enabled for a cocktail of insensitive antibodies which bind each one of the free cTnI, binary complexed cTnI, and ternary complexed cTnI for use in a method of determining the presence of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample.

In view of the teachings of In re Wands, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue. It has been set forth above that 1) the experimentation required to enable a single insensitive antibody to determine the presence of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample, would be great as 2) there is no experimental evidence provided that would indicate that the claimed method would work using a single insensitive antibody; 3) there is no proper guidance that shows that a single insensitive antibody has been generated, characterized, and selected to bind each and all of free cTn, binary complexed cTn and ternary complexed cTn, 4) the

nature of the invention is a cocktail of antibodies which bind each one of the free cTnI, binary complexed cTnI, and ternary complexed cTnI for use in a method of determining the presence of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample, 5) the relative skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by the fact that no prior art has been cited that shows generation, characterization, and selection of an antibody that has specific binding for each and all of free cTn, binary complexed cTn, and ternary complexed cTn , and lastly 7) the claims broadly recite a single insensitive antibody which binds each one of free cTnI, binary complexed cTnI, and ternary complexed cTnI for use in a method of determining the presence of all of free cTnI, binary complexed cTnI, and ternary complexed cTnI in a sample, without specifically stating how this can be done without undue experimentation.

Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

Response to Arguments and Declaration

4. Applicant's arguments filed 1/9/03 have been fully considered but they are not persuasive.

A) Applicant argues that Examiner is incorrect in stating that the invention is directed to a cocktail of antibodies having specific binding for each of the free cTnI, binary complex of cTnI, and ternary complex of cTnI" because the present invention is

directed to providing one or more antibodies that are insensitive with respect to binding with free cTnI, binary complex of cTnI, and ternary complex of cTnI.

Contrary to Applicant's argument, claim 71 is directed to "two or more antibodies ... that is insensitive with respect to each form of free cTnI, cTnI in a binary complex with troponin C, and cTnI in a ternary complex with troponin C and troponin T" and claims 79, 80, 81, 88, and 91 are directed to "two or more antibodies ... which bind to each form of free cTnI, cTnI in a binary complex with troponin C, and cTnI in a ternary complex with troponin C and troponin T". Further, page 6 of the specification provides that an "insensitive antibody" is one that will tend to bind more than one form of troponin, i.e. each one of free cTnI, cTnI in a binary complex with troponin C, and cTnI in a ternary complex with troponin C and troponin T, as recited in the claims.

B) Applicant disagrees in Examiner's contention that there is no predictability based on the instant specification that a single antibody has binding for each of the free, binary, and ternary complexed isoforms of cTnI. Applicant, therefore, provided a declaration of Dr. Kenneth Buechler describing why those of ordinary skill in the art would readily acknowledge that antibodies, which are insensitive with respect to the complexed state of cTnI can be produced using only routine methods well known in the art. According to Applicant, cTnI contains certain antigenic sites that are cardiac specific and antibodies directed to these sites are used to determine cTnI. Antibodies to these sites can therefore be used to identify and bind the free, binary, and ternary

complexed isoforms of cTnI. Applicant points to page 24, lines 21-29 to support their statement.

In response, page 24, lines 21-29 provides that the immunoassay can be formulated with specific antibodies that recognize epitopes of the troponin I and T in the complexed and also unbound troponin I and T. However, it does not provide that the antibodies can recognize epitopes of troponin I and T in the unbound form and then both of the binary and the ternary forms, which is encompassed by the scope of the rejected claims.

In response to Applicant's statement in the declaration provided by Dr. Kenneth Buechler describing that those of ordinary skill in the art would readily acknowledge that the claimed antibody can be produced using only routine methods well known in the art, Applicant fails to provide evidentiary showing such as in the form of data, that supports generation, selection, and use of this antibody having conserved epitope that will bind each one of the unbound cTnI, cTnI in a binary complex form, and cTnI in a ternary complex form for use in an assay. Likewise, nowhere in the specification provides equivalent support of the generation, selection, and use of an antibody having conserved epitope that will bind each one of the unbound cTnI, cTnI in a binary complex form, and cTnI in a ternary complex form for use in an assay.

C) Applicant disagrees in Examiner's contention that the specification fails to provide guidance to enable the claimed method to make and use a single antibody that specifically binds all of the free, binary, and ternary complexed forms of cTnI. Applicant

specifically argues that the specification describes methods for obtaining antibodies that are insensitive to the complex state of cardiac specific troponin isoforms, such as in page 21, line 3, through page 22, line 19.

In response, page 21, line 3 to page 22, line 19 provides generation and selection of antibodies that are preferentially either sensitive or insensitive to the binding of troponin I or T in binary complexes. It further provides generation and selection of antibodies that are preferentially either sensitive or insensitive to the binding of troponin I or T in ternary complexes. The antibodies are generated and selected by first screening for affinity and specificity with the purified binary or ternary complexes. However, nowhere in the specification specifically shows of any generation and selection of an insensitive antibody having a conserved epitope that binds each one of the free, binary, and ternary complexed form of cTnI or cTnT, to encompass that the scope of the claimed invention.

D) Applicant disagrees in Examiner's contention that there are no working examples in the specification that show results using a single antibody which is encompassed by the broad scope of the claims, i.e. antibody that binds each one of free, binary, and ternary complexes of cTn. Applicant points to Example 10 in the specification for a description of certain antibodies that are demonstrated to bind both of free and binary complexes of cTnI equally well. Applicant also notes that in the specification at page 62, lines 20-24, a skilled artisan would understand that the antibodies must bind both of free and binary complexes to form a sandwich assay.

Applicant also points to Example 17 in the specification for a description of certain antibodies that are demonstrated to bind both of free and ternary forms of cTnT for use in a sandwich assay.

In response, Example 10 tests both monoclonal and polyclonal antibodies for their capacity to bind free cTnI and cTnI bound to cTnC in a binary complex, and found in page 63, lines 20-24 that some antibodies do bind free cTnI and binary complex forms of cTnI, equally well. Examples 17 and 23 also tests both monoclonal and polyclonal antibodies for their capacity to bind free cTnT, cTnT bound to cTnC and cTnT in a ternary complex, and found that some antibodies do bind free cTnT and ternary complex forms of cTnT, equally well. However, nowhere in Example 10 or Example 17 and 23 specifically provides an insensitive antibody generated and selected to bind any and all of free, binary, and ternary complexed forms of cTnI or cTnT, to encompass that the scope of the claimed invention.

E) Applicant disagrees in Examiner's contention that the quantity of experimentation necessary to produce and identify antibodies that are insensitive to the complexed state of cTn isoforms would be undue. Applicant further note in the declaration that methods for identifying antibodies that are insensitive to the complexed state of cTn isoforms are described in detail throughout the specification.

In response, the specification including all those noted and pointed out by Applicant in the arguments and declaration provide a description and use of antibodies that are demonstrated to bind free and a binary form of cTnI **or** free and a ternary form

of cTnI. However, nowhere in the specification provides or shows insensitive antibodies that are insensitive to each one of the unbound, binary, and ternary complexed states of cTnI, and which are generated and selected to bind all of free, binary, and ternary complexed form of cTnI or cTnT, to encompass that the scope of the claimed invention.

F) Applicant noted in item no. 9 of the declaration that the phrase "an antibody" recited in the claims would not be understood by the skilled artisan to imply a single molecule of antibody.

In response to Applicant's statement in the declaration, "an antibody", "a molecule", or "a cell" denotes a singular form of an element and does not necessarily imply a population, i.e. antibodies, molecules, cells. Alternatively, antibodies, molecules, or cells in a population are referred to as "antibodies", "molecules", or "a population of cells", set forth in a plural form, if so intended.

Allowable Subject Matter

5. Claims 71-74 are allowable. Claims 84, 85, 90, and 93 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday-Thursday, 6:30-1630, and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-0169.

Gailene R. Gabel
March 20, 2003

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP 1800/1641
3/21/03